Recommendations and Guidelines

Management of challenging cases of patients with cancer-associated thrombosis including recurrent thrombosis and bleeding: guidance from the SSC of the ISTH

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Scope and methodology

This article gives guidance on common clinical problems complicating the management of anticoagulation in patients with cancer-associated thrombosis (CAT). Although low molecular weight heparins (LMWHs) have improved patient outcomes and simplified therapy, high-quality evidence on the optimal management of CAT is lacking. This guidance statement will specifically address: (i) the treatment of recurrent venous thromboembolism (VTE) with dose escalation of LMWH; (ii) management in patients with thrombocytopenia; (iii) management in patients with active bleeding; and (iv) the role of inferior vena caval (IVC) filters. It will also discuss the use of novel oral anticoagulants (NOACs) for the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE). Some of these topics are covered in published consensus guidelines [1–5], but the aim of this guidance statement is to outline expert experience and the biological rationale that may influence decision-making, and offer concrete approaches to the management of anticoagulation in individual cancer patients with these therapeutic challenges. Recognizing the lack of high-quality evidence in many of these areas, it is important for patients to be informed of the uncertainties, risks and benefits of the management plan, and for proper documentation of the discussion to be included in the medical chart.

The guidance statements included in this document are similar to those in other guidance documents, and are predicated on the following premises [6]:

1. For each of the clinical situations, our guidance statements are applicable to an average patient with cancer-associated DVT and/or PE. We anticipate that there will be clinical circumstances for which our guidance statements do not apply. As for all cases, our statements may provide guidance but do not replace clinical judgement for the management of individual patients.
2. The wording ‘we recommend’ reflects a strong guidance statement with strong consensus among the panel members, whereby the clinician should consider adopting the practice in a majority of cases.
3. The wording ‘we suggest’ reflects a weak guidance statement with moderate consensus among the panel members, whereby the clinician may adopt the guidance statement or use an alternative approach to manage patients.

Definition of terms

The definitions of terms used in this guidance manuscript are:

1. CAT: symptomatic proximal lower limb DVT (involving the popliteal vein or more proximal vessels) or PE (involving a segmental or more proximal pulmonary artery). The guidance statement does not apply to treatment of VTE in unusual sites, including splanchnic, cerebral or upper extremity vein thrombosis, or to arterial thrombotic events.
2. Acute CAT: diagnosis of the index DVT or PE was made within the past 1 month.
3 Subacute CAT: diagnosis of the index DVT or PE was made between 1 and 3 months ago.
4 Chronic CAT: diagnosis of the index DVT or PE was made > 3 months ago.

Management of recurrent CAT despite anticoagulation

Recurrent VTE despite appropriate anticoagulation is common among cancer patients. Gender, tumor type, TNM staging and prior history of VTE seem to be important predictors of recurrent VTE in cancer patients [7]. Approximately 10–17% of patients with CAT treated with a vitamin K antagonist (VKA) and 6–9% of patients treated with LMWH will have recurrent VTE during follow-up [8–10]. The causes for VKA failure are multifactorial, and cancer patients can develop recurrent VTE despite maintaining therapeutic International Normalized Ratio (INR) values [11]. LMWHs for at least the first 3 months are known to be more effective than VKAs in the treatment of CAT [8–10], and observational studies have also shown that switching cancer patients with recurrent VTE on VKAs to therapeutic doses of LMWH is safe and effective [12,13].

Raising the anticoagulation target of the VKA (e.g. INR 2.5–3.5) is not recommended, given the lack of cancer-specific data and the heightened risk of bleeding with a higher target INR [11,14].

Mechanisms for LMWH failure have not been studied. One retrospective cohort study has shown that dose escalation of LMWH (~25% or increased to weight-adjusted therapeutic doses if the patients is receiving lower doses) in cancer patients with recurrent VTE is effective and safe [12]. It is not known whether dividing the escalated dose of LMWH into a twice-daily regimen is more efficacious.

An empirical approach to managing cancer patients with symptomatic recurrent VTE despite anticoagulation has been proposed [15,16]. It is important to confirm drug compliance and ensure that heparin-induced thrombocytopenia (HIT) has been excluded. Patients with CAT who are being treated with VKAs should be switched to LMWH, and those managed with LMWH should have their dose increased by 25% (or increased to therapeutic, weight-adjusted doses if they are receiving lower doses). All patients should be reassessed in 5–7 days to ensure symptomatic improvement. Patients without symptomatic improvement should be considered for another dose escalation, and the anti-FXa level can be used to estimate the next dose escalation. For a once-daily regimen, clinicians should aim for a peak anti-FXa level of 1.6–2.0 U mL⁻¹ whereas for a twice-daily regimen, a level of 0.8–1.0 U mL⁻¹ is suggested [15,16].

These values are empirical, and have not been assessed in clinical trials. Checking anti-FXa levels is not routinely recommended for dose adjustment, because there is weak correlation with clinical outcomes.

Other therapeutic options, including the insertion of an IVC filter or switching to a different anticoagulant (e.g. fondaparinux or VKA), have been proposed. However, there are no published data on their efficacy in treating cancer patients with symptomatic recurrent VTE despite LMWH administration. The insertion of an IVC filter in addition to anticoagulation provides no net benefit to patients in preventing recurrent thrombosis, and has no impact on patient survival (see below) [17–21]. Fondaparinux and VKAs are associated with a higher risk of recurrent thrombosis than LMWH in patients with CAT [9,22]. Therefore, these therapeutic options are not recommended.

Guidance statement:

1. We recommend that cancer patients with symptomatic recurrent VTE despite therapeutic anticoagulation with VKAs be switched to therapeutic weight-adjusted doses of LMWH.
2. We suggest that cancer patients with symptomatic recurrent VTE despite anticoagulation with LMWH continue with LMWH at a higher dose, starting at an increase of ~25% of the current dose or increasing it back up to the therapeutic weight-adjusted dose if they are receiving non-therapeutic dosing.
3. We recommend that all cancer patients with recurrent VTE despite anticoagulation be reassessed 5–7 days after a dose escalation of their anticoagulant therapy.

Patients with symptomatic improvement should continue with the same dose of LMWH and resume their usual follow-up. In patients without symptomatic improvement, we suggest using the peak anti-FXa level to estimate the dose of the next escalation.

Management of CAT in patients with thrombocytopenia

Thrombosis is commonly diagnosed in patients with malignancy and thrombocytopenia [23], but the literature on management is scarce [9,24]. In order to tailor the therapeutic strategy, clinicians need to assess: (i) the possible etiology of the thrombocytopenia (e.g. HIT, thrombotic thrombocytopenic purpura, immune thrombocytopenia, or chemotherapy effect); (ii) the severity; (iii) the expected duration and course (for example, whether the thrombocytopenia is transient or permanent, and whether the current platelet count is the nadir or it will drop further); (iv) whether there are potentially reversible causes that can be corrected; and (v) whether there are other risk factors for bleeding, such as advanced age or renal insufficiency. Anticoagulation in patients with thrombocytopenia should be applied on an individual patient basis after assessment of the risks and benefits, and taking into account the direction of care and patient preference.

For situations when the use of anticoagulant therapy is considered, it is important to weigh the relative risks of recurrent thrombosis and serious bleeding. In the initial month (acute period) following the diagnosis of VTE, the risk of recurrent thrombosis is highest [8,9]. Consequently, giving maximal or therapeutic anticoagulant therapy is important. In patients with acute CAT and a platelet count of ≥50 × 10⁹ L⁻¹, full therapeutic anti-
agulation without platelet transfusion is appropriate. However, in patients with a platelet count of \(< 50 \times 10^9 \text{L}^{-1}\), platelet transfusion support to maintain a platelet count of \(\geq 50 \times 10^9 \text{L}^{-1}\) to allow full, therapeutic anticoagulation should be considered [23]. Hospitalization is required unless there is adequate and timely support for outpatient transfusion and close monitoring. If platelet transfusions are not possible or are contraindicated, we suggest insertion of a retrievable IVC filter, which should be removed when platelet recovery (> 50 \times 10^9 \text{L}^{-1}) is achieved and anticoagulation can resume. The cut-off of 50 \times 10^9 \text{L}^{-1} is empirical, but there is general consensus that the risk of spontaneous bleeding is very low above this level.

In the subacute or chronic treatment periods, when the risk of VTE recurrence is not as high, published data provide weak support for LMWH dose reduction in patients with thrombocytopenia (\(< 50 \times 10^9 \text{L}^{-1}\)) [24,25]. Platelet transfusion is probably not warranted. Consequently, in patients with a platelet count between 25 \times 10^9 \text{L}^{-1} and 50 \times 10^9 \text{L}^{-1}, clinicians can consider reducing the dose of LMWH by half or using a prophylactic dose of LMWH, depending on individual patient characteristics (e.g. tumor burden, clot burden, and risk factors for bleeding) [9,24,26]. In patients with a platelet count of \(< 25 \times 10^9 \text{L}^{-1}\), withholding anticoagulant therapy might be prudent. However, prophylactic doses of LMWH have been used safely in patients with a platelet count of \(< 25 \times 10^9 \text{L}^{-1}\) and can improve symptoms [27,28].

Guidance statement:

1. We recommend giving full therapeutic doses of anticoagulation without platelet transfusion in patients with CAT and a platelet count of \(\geq 50 \times 10^9 \text{L}^{-1}\).

2. For acute CAT and thrombocytopenia (\(< 50 \times 10^9 \text{L}^{-1}\)):
   - i. We recommend full therapeutic doses of anticoagulation with platelet transfusion to maintain a platelet count of \(\geq 50 \times 10^9 \text{L}^{-1}\).
   - ii. If platelet transfusion is not possible or is contraindicated, we suggest insertion of a retrievable filter and removal of the filter when the platelet count recovers and anticoagulation can be resumed.

3. For subacute or chronic CAT and thrombocytopenia (\(< 50 \times 10^9 \text{L}^{-1}\)):
   - i. We suggest reducing the dose of LMWH to 50% of the therapeutic dose or using a prophylactic dose of LMWH in patients with a platelet count of 25–50 \times 10^9 \text{L}^{-1}.
   - ii. We suggest discontinuing anticoagulation in patients with a platelet count of \(< 25 \times 10^9 \text{L}^{-1}\).

Management of CAT in patients who are bleeding

Major or serious bleeding episodes occur in \(\sim 7\%\) of patients with CAT on anticoagulation [8–10]. Cancer-specific factors (e.g. tumor type, location, and metastatic disease), treatment-specific factors (e.g. chemotherapy-induced thrombocytopenia), poor nutritional status (hypalbuminemia), impaired renal function and the need for more frequent invasive procedures all contribute to increasing the risk of bleeding in cancer patients [16]. Recent major bleeding, renal dysfunction (creatinine clearance of \(< 30 \text{mL min}^{-1}\)), immobility (\(\geq 4\) days), metastatic disease and low body weight (\(< 60 \text{kg}\)) have been identified as important predictors of major bleeding complications and of fatal bleeding in cancer patients [29,30].

As in any patient with active bleeding, clinicians need to assess, identify and control the source of bleeding whenever possible. Supportive treatments (e.g. red blood cell transfusion) should be given when required. Patients with CAT who have active major bleeding (e.g. not amenable to intervention, in a critical site, or life-threatening) should have their anticoagulation withheld. In those who are also at high risk of recurrent VTE (e.g. acute or subacute CAT), insertion of an IVC filter could be considered. In patients who are not at high risk of recurrent VTE (e.g. chronic CAT), filter insertion is not recommended. Once the bleeding has resolved, anticoagulation can be initiated or resumed, and the IVC filter, if inserted, should be removed. The decision on initiating or resuming anticoagulation following an episode of intracranial bleeding should be made in collaboration with the neurologist or neurosurgeon.

Minor bleeding (e.g. minor epistaxis) during anticoagulation will usually occur without any significant physiological or symptomatic consequences. In our experience, most patients with minor bleeding will tolerate anticoagulation, but it is recognized that such experience is subjective and will vary between patients.

Guidance statement:

1. We recommend careful and thorough assessment of each bleeding episode, including identification of the source, its severity or impact, and reversibility.

2. We recommend usual supportive care with transfusion and surgical intervention to stop the bleeding, whenever indicated and possible.

3. We recommend withholding anticoagulation in patients who have a major or life-threatening bleeding episode.

4. We suggest IVC filter insertion in patients with acute CAT or subacute CAT who are having a major or life-threatening bleeding episode.

5. We recommend against IVC filter insertion in patients with chronic CAT.

6. We recommend initiating or resuming anticoagulation and removing the retrievable IVC filter (if inserted) once the bleeding resolves.

Role of IVC filters

The rationale for IVC filter insertion is to prevent or reduce the risk of fatal or clinically significant PE from a
large embolus arising from thrombus in the veins of the pelvis or lower limbs. Consequently, filter insertion is commonly performed in the setting of recurrent PE or DVT extension despite anticoagulation, and in patients with an acute PE or DVT who also have a contraindication for anticoagulation. However, evidence from large observational studies [19,21] and randomized controlled trials [17,18,20] for the efficacy of filters in reducing fatal PE is lacking. Furthermore, a reduction in non-fatal PE occurs at the cost of an increase in recurrent DVT [17,20].

The use of IVC filters in cancer patients is controversial and is a frequently encountered clinical problem, because of the high risk of recurrent VTE and bleeding in these patients. Data in cancer patients are limited to a small clinical trial that showed no benefit with IVC insertion in addition to anticoagulation with fondaparinux [18], and retrospective studies showing high rates of lower limb DVT following filter insertion [21]. This high rate of DVT in the setting of IVC insertion is reflective of the persistently heightened prothrombotic state in cancer patients, which is not suppressed by IVC filters. Indeed, filter thrombus and fatal PE are not uncommon in cancer patients with filter placement [21,31]. More recently, serious safety concerns over embolization, fracturing and migration of retrievable filters have been raised [32,33], prompting clinicians to rethink the indications for filter insertion and to remove retrievable filters as soon as the indication has resolved.

In summary, considering that filter insertion does not reduce morbidity or mortality, does not suppress hypercoagulability in patients with cancer, and is associated with serious complications and cost, the panel’s consensus is that IVC filters should not be systematically inserted in cancer patients with recurrent VTE, and that their use should be limited to situations where one or more strong contraindications to anticoagulation exist and the risk of potentially fatal PE is high. If a filter is inserted, it is prudent to reintroduce anticoagulation when it is safe to do so, in order to suppress the underlying hypercoagulable state and reduce the risk of further DVT or PE.

Guidance statement:
1. We recommend against IVC filter insertion in the absence of contraindications to anticoagulation.
2. We suggest IVC filter insertion in cancer patients with contraindications to anticoagulation and a high risk of potentially fatal PE.
3. We recommend resuming anticoagulation with LMWH and removing the retrievable filter in cancer patients when the contraindication has resolved.

Role of the NOACs in the management of CAT

Recently, new oral direct FXa inhibitors (rivaroxaban, apixaban, and enoxaparin) and a direct thrombin inhibitor (dabigatran) have been developed, and some are approved for the acute and long-term treatment of VTE [34–38]. The NOACs represent an attractive option for the treatment of CAT, because they are taken orally at fixed doses without the need for laboratory monitoring. Unfortunately, there are no published data on the efficacy and safety of the NOACs in the management of CAT. In the clinical trials evaluating NOACs in DVT and PE treatment, only 0.1–6.8% of patients randomized to receive a NOAC had a diagnosis of cancer (~300 patients) [34–38]. The acute VTE trials compared a NOAC with initial LMWH with transition to a VKA (rather than LMWH monotherapy), and the extended therapy trials compared a NOAC with placebo. Given the higher risk of recurrent thrombosis despite anticoagulation and the higher risk of anticoagulant-related bleeding in cancer patients, we cannot assume that the efficacy and safety outcomes observed in these trials of largely non-cancer patients also apply to cancer patients. Furthermore, indirect, post hoc data from trials comparing fondaparinux or rivaroxaban with enoxaparin suggest that specific FXa inhibition might be less efficacious than LMWH inhibition in cancer patients [22,39]. Although the oral route of administration is more comfortable than injections, it may not be ideal in patients with nausea, vomiting, and diarrhea, which are common side effects of chemotherapy. Also, gastrointestinal absorption and bioavailability may be altered in patients with mucositis or diarrhea, and gastrointestinal bleeding may be more frequent with NOACs [40]. None of these agents have an antidote to rapidly reverse the anticoagulant effect, and there is a lack of experience in managing these agents in the perioperative/procedural period and in patients with thrombocytopenia. Although NOACs have fewer drug interactions than warfarin, their dependence on the P-glycoprotein transport and CYP3A4 metabolic pathways for their uptake and clearance must be considered in cancer patients. Different chemotherapy agents may induce (e.g. dexamethasone, doxorubicin, and vinblastine) or inhibit (e.g. tamoxifen, cyclosporine, sunitinib, and other tyrosine kinase inhibitors) these pathways, leading to potentially clinically important changes in drug levels which may predispose patients to higher risks of recurrent thrombosis or bleeding [16]. Finally, the lack of assays for measuring the anticoagulant effect of the NOACs poses challenges in the management of cancer patients presenting with recurrent VTE or with serious bleeding. Given these important limitations and the lack of cancer patient-specific data, we discourage the use of NOACs in cancer patients [4].

Guidance statement:
1. We recommend against the use of NOACs for the initial and/or long-term treatment of CAT.
2. We recommend investigating the efficacy and safety of NOACs in randomized, controlled clinical trials specifically in cancer patients with VTE, with particular emphasis on drug–drug interactions with antineoplastic agents.
Addendum
M. Carrier, A. Khorana and A. Lee: designed the study, collected literature, analyzed and interpreted data, and wrote the manuscript. J. Zwicker and S. Noble: designed the study, collected literature, analyzed and interpreted data, and critically revised the intellectual content.

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The authors state that they have no conflict of interest.

References
23 Gerber DE, Segal JB, Levy MY, Kane J, Jones RJ, Streiff MB. The incidence of and risk factors for venous thromboembolism (VTE) and bleeding among 1514 patients undergoing


